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# Obesity, bone density relative to body weight and prevalent vertebral fracture at age 62 years: the Newcastle Thousand Families Study

H.A. Rudman [1], F. Birrell [2], M.S. Pearce [3], S.P. Tuck [2], R.M.Francis [3], L. Treadgold [1], K. Hind [2, 4]

[1] Leeds Institute of Cardiovascular & Metabolic Medicine, University of Leeds, Leeds, United Kingdom.

[2] Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, United Kingdom.

[3] Institute of Health and Society, Newcastle University, Sir James Spence Institute of Child Health, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom.

[4] Department of Sport and Exercise Sciences, Durham University, County Durham, United Kingdom.

For correspondence: Dr K Hind PhD, CCD. Assistant Professor of Sport and Exercise Sciences, and Fellow of the Wolfson Research for Health and Wellbeing, Department of Sport and Exercise Sciences, Durham University, 42 Old Elvet, Durham, DH1 3HN. United Kingdom.

Telephone: +44 191 334 6837

Email: karen.hind@durham.ac.uk

**Abstract**

Obesity is a global epidemic and there remains uncertainty over the effect of obesity on skeletal health, particularly in the context of osteoporosis. The aim of this study was to investigate associations of body mass index (BMI) and obesity with bone mineral density (BMD) and prevalent vertebral fracture (VF) in men and women aged 62 years. Three hundred and forty two men and women aged 62.5 ± 0.5 years from the Newcastle Thousand Families Study birth cohort, underwent DXA evaluations of femoral neck and lumbar spine BMD, and of the lateral spine for vertebral fracture assessment. The likelihood of prevalent VF was significantly increased in men when compared to women (OR = 2.7, $p < 0.001$, 95% Cl 1.7– 4.4). As BMI increased in women, so did the likelihood of prevalent any-grade VF (OR = 1.09, $p = 0.006$, 95% CI 1.02 – 1.17). Compared to normal weight women, obese women were more likely to have at least one VF (OR = 2.65, $p = 0.025$, CI 1.13 – 6.20) and at least one grade 1 VF (OR = 4.39, $p = 0.005$, CI 1.57 – 12.28). Obese men were more likely to have a grade 2 and/or 3 VF compared to men of normal weight (OR = 3.36, $p = 0.032$, CI 1.11 – 10.16). In men and women, BMI was negatively associated with femoral neck BMD/ weight (R = - 0.65, R = - 0.66, $p < 0.001$) and lumbar spine BMD/ weight (R = - 0.66, R = - 0.60, $p < 0.001$). Obesity appears to be a risk factor for prevalent VF, and although absolute BMD is higher in obese individuals, the increase does not appear commensurate to their increase in body weight.

**Keywords:** *obesity; bone; fracture; DXA; fat.*

## Introduction

Obesity is a global epidemic, with worldwide rates having more than doubled since 1980 (1). Despite efforts to improve diet and exercise behaviours within the UK population, obesity remains commonplace with 26% of adults documented as having an obese body mass index (BMI) in the 2016 Health Survey for England (2). Our understanding of the implications of obesity on cardiovascular health, diabetes and other common comorbidities is comprehensive and well-publicised. However, there remains uncertainty over the effect of obesity on skeletal health, particularly in the context of osteoporosis.

Osteoporosis is a systemic skeletal disorder characterised by compromised bone strength, predisposing to an increased risk of fracture (3). Fractures occur when mechanical loading exceeds the functional capacity of bone and those resulting from low trauma injuries represent the clinical end point of osteoporosis. Of all osteoporotic fractures, those affecting the vertebrae are the most common, but vertebral fractures are also the most poorly detected and predicted (4, 5). Vertebral fractures are predominantly low trauma injuries, precipitated by everyday activities such as bending to lift light objects or falling from standing (5), although they can result from high impact forces to the spine (6). They are associated with increased morbidity, reduced quality of life and a significant economic burden, costing around €1,745 million in Europe in the year 2010 (7). While deformities can present clinically as back pain, they are commonly asymptomatic and under-diagnosis is a worldwide problem (5).

Understanding the risk factors and improving the identification of vertebral fractures is important because even mild deformities are associated with an elevated risk of future vertebral, and other osteoporotic fractures (8). Epidemiological research indicates that the prevalence and number of vertebral fractures increases with age in both sexes (9), and recent

data show that in the United Kingdom, the rate of clinical vertebral fracture is greater in women than in men over the age of 50 years (10).

Body weight is positively associated with bone mineral density (BMD), which is an established measure of bone strength (11). A reduction in body weight results in bone loss (12) and low BMI is an established risk factor for osteoporotic fractures, especially those at the hip (13, 14). As such, low BMI is considered in fracture risk prediction algorithms including FRAX and Garvan, with the highest gradient of risk seen at BMI levels less than 20 $kg/m^2$ (14). However, few studies have looked at BMD in relation to body weight (6) and there continues to be uncertainty about the relationship between obesity and fracture risk.

Accumulating evidence indicates that the relationship between BMI and fracture varies according to fracture site. Whereas the risk of hip fracture is known to be highest among underweight individuals (14), fractures of the ankle, lower limb and upper arm have been found to be more common in obese than non-obese or underweight postmenopausal women (15, 16). Clinically diagnosed fractures of the vertebrae have been reported to be lower in obese women (16), but it is known that a large proportion of vertebral fractures remain clinically undetected (17, 18). This relationship is understudied in men, for whom results have been discordant (19, 20).

The purpose of this study was to explore BMD relative to body weight, and the prevalence of vertebral fracture, in a cohort of men and women according to BMI and BMI category.

## Materials and Methods

### *Participants*

The research was conducted as a cross-sectional analysis of 342 participants from the Newcastle Thousand Families Study (NTFS) birth cohort. The NTFS was initiated in 1947 by

Sir James Spence, when 1,142 children born in May and June of that year to mothers resident in the city of Newcastle upon Tyne were recruited in response to the high infant mortality rate and poverty levels. The birth cohort has been followed up at regular intervals with a multidisciplinary research focus and the cohort has been described in detail at age 50 years (21). The current study evaluated participants during the most recent NTFS follow up wave in 2011. 37% of those presumed to still be alive at the end of the follow-up period returned for a clinical examination having completed health and lifestyle questionnaires. A favourable ethical opinion was obtained from the Sunderland Local Research Ethics Committee (Reference 09/H0904/40) and all included study members gave their written consent.

*Clinical measurements*

Participants were assessed in light-weight clothing with shoes and jewellery removed. Body weight was measured to the nearest 0.1kg using electronic calibrated scales (with heavy clothing and shoes removed). Standing height was measured to the nearest 0.1 cm using a stadiometer (with shoes removed). BMI ($kg/m^2$) was subsequently calculated [weight (kg)/height$(m)^2$]. BMI scores were categorised according to the WHO criteria as normal weight (18.5-24.99 $kg/m^2$), overweight (25-29.99 $kg/m^2$) and obese (>30 $kg/m^2$) (22). One female subject had been excluded from further analysis as the only participant calculated to have an underweight BMI (<18.5 $kg/m^2$).

Fan beam dual energy X-ray absorptiometry (Lunar iDXA, GE Healthcare, Madison, WI) was used to evaluate left femoral neck BMD, lumbar spine BMD (L1-L4) and prevalent VF. Daily calibration and DXA quality control observations were recorded as per the manufacturer's guidelines for the duration of the data collection, with no equipment drifts or faults reported. Precision error for iDXA measurements are 0.4% coefficient of variation (CV) for lumbar spine BMD and 0.9% CV for femoral neck BMD (23). Patient positioning

for the femoral neck BMD scan was assisted using the GE-dual femur positioning device which allows both legs to be abducted and inwardly rotated 25$^{o}$.

Vertebral fracture prevalence was assessed using a lateral vertebral scan and vertebral fracture assessment (VFA) software (EnCore version 15.0). VFA, as described by the International Society for Clinical Densitometry (ISCD), denotes the use of densitometric spinal imaging for the purpose of identifying VFs (17). The method has been shown to be equally as accurate as plain radiography (24) and is regarded as an effective method for diagnosing and reporting VFs (17, 25). DXA scans were performed with participants in the left lateral decubitus position, as recommended by the manufacturer (participants lay on their left side with their knees and hips flexed at a $90^{0}$ angle and arms flexed with both hands joined together near the head). All scans began at the sacrum, targeting the T4-L4 segment of the spine. Regions of interest and bone edge markers were verified or corrected where required, by a certified clinical densitometrist (ISCD) with specific training in VFA. Verification included the observation of correct placement of markers on the vertebral bodies and differentiation between genuine VFs and deformities with other causes such as degenerative disease. Measurements were compared with those of other vertebrae, allowing the software to estimate the extent of any reduction in the anterior, middle or posterior vertebral height. VFs were subsequently graded according to their severity as grade 1 (mild), grade 2 (moderate) and grade 3 (severe) using the method set out by Genant et al (26). Grade 1 corresponds to a 20 to 25% reduction in any vertebral height; grade 2 a 25 to 40% reduction in vertebral height and grade 3 represents a >40% reduction in vertebral height.

*FRAX scores*

In addition to age, sex and BMI, individual FRAX scores were included in the analyses (27) . Information on previous fracture, parent hip fracture, current smoking, rheumatoid arthritis,

glucocorticoid use, secondary osteoporosis, and alcohol consumption, were self-recorded by participants in the NTFS general health questionnaire. FRAX scores indicating the 10 year probability of a major osteoporotic fracture were subsequently calculated from femoral neck BMD and the aforementioned clinical risk factors.

*Statistical analysis*

The data were analysed using STATA software, version 12.0 (StataCorp, College Station, TX). Ratios were created to express lumbar spine BMD as well as femoral neck BMD relative to participant body weight as follows:

$$[\text{BMD} / \text{body weight (kg)}] \times 100$$

Descriptive statistics including the mean and standard deviation (SD) were produced for all measurements. Logistic regression was used to determine the associations of sex, BMI and BMD / weight with the prevalence of VF, producing estimated odds ratios (OR). All models were sex-specific and adjusted for lumbar spine BMD. Moderate and severe fractures (grade 2-3) are more reliable indicators of underlying disease than mild fractures (grade 1) when using VFA (28). Hence the presence of a moderate or severe fracture was analysed separately. Independent samples t-tests were used to determine whether differences in anthropometric characteristics of those with and without fractures were significant.

Spearman's and Pearson's correlative analyses were used to examine associations between BMI, BMD, FRAX scores, BMD/weight ratios and VF. One-way ANOVA models with post-hoc Tukey analysis were used to determine significant differences in the BMD/weight ratios of men and women of differing BMI categories. Statistical significance was set at $p = 0.05$.

## Results

The mean age of the cohort at the time of testing was 62.5 ± 0.5 years. There were fewer male (44% v 51%) and more female (49% v 56%) participants in the current sample compared to the original 1947 cohort (p = 0.008). More than half of the women were using hormone replacement therapy (HRT) (60%), as has previously been reported in U.K. cohorts (29). History of previously diagnosed fracture was reported by 15.8% of men and 16.8% of women. Six men and five women had previously had a clinically diagnosed vertebral fracture. Two men and one woman had previously suffered a hip fracture. Sex-specific anthropometric and bone density results are given in Table 1.

**Table 1.** Anthropometric and bone mineral density (BMD) summaries for men and women aged 62 years

| | **Women** n = 190 *(mean ± SD)* | **Men** n = 152 *(mean ± SD)* | ***p*** |
|---|---|---|---|
| Body weight (kg) | 73.8 ± 15.1 | 84.3 ± 15.2 | < 0.001 |
| Height (cm) | 162.1 ± 6.9 | 173.5 ± 7.1 | < 0.001 |
| Body mass index (kg/m$^2$) | 28.0 ± 5.3 | 28.0 ± 4.7 | 0.929 |
| Femoral neck BMD (g/cm$^2$) | 0.927 ± 0.143 | 0.944 ± 0.139 | 0.238 |
| Lumbar spine (L1-L4) BMD (g/cm$^2$) | 1.112 ± 0.180 | 1.204 ± 0.160 | < 0.001 |
| Femoral neck BMD / weight (g/cm$^2$ : kg) | 1.29 ± 0.27 | 1.15 ± 0.26 | < 0.001 |
| Lumbar spine BMD / weight (g/cm$^2$ : kg) | 1.55 ± 0.32 | 1.47 ± 0.30 | 0.015 |
| FRAX Major Osteoporotic Fracture | 8.2 ± 3.83 | 6.74 ± 3.83 | < 0.001 |

*Bone mineral density*

Women had lower lumbar spine BMD than men, although men had lower lumbar spine BMD/ weight (Table 1). In men and women, BMI was negatively associated with femoral

neck BMD/ weight (R = - 0.65, R = - 0.66, $p < 0.001$) and lumbar spine BMD/ weight (R = - 0.66, R = - 0.60, $p < 0.001$). Scatter graphs illustrating the association between BMD/weight and BMI in men and women are shown in Figure 1.

Lumbar spine BMD/ weight and femoral neck BMD/ weight of men and women by BMI category are given in Table 2. Both lumbar spine BMD/ weight (F=37.78, $p < 0.001$) and femoral neck BMD/ weight (F=34.93, $p < 0.001$) varied across BMI category in men. Lumbar spine BMD/ weight (F=39.16, $p < 0.001$) and femoral neck BMD/ weight (F=56.44, $p < 0.001$) also varied across BMI category in women. Lumbar spine BMD/ weight and femoral neck BMD/ weight were significantly lower in overweight and obese men and women compared to those of normal weight (all $p < 0.001$). Lumbar spine and femoral neck BMD/ weight were also lower in men and women who were obese compared to those who were overweight (all $p < 0.001$).

*Sex-specific vertebral fracture prevalence*

The prevalence of any-grade VF was 48.0% in men and 25.3% in women. Men were more than twice as likely to have at least one prevalent VF (OR = 2.7, $p < 0.001$, 95% Cl 1.7– 4.4). The prevalence of grade 1 vertebral deformities was higher in men compared to women (38.2% v 19.5%). Men were also more than three times as likely to have at least one grade 2-3 VF (OR = 3.5, $p < 0.001$, 95% CI 1.9 – 6.5). The prevalence of grade 2 and/or grade 3 VF was 27.0% (n = 41) in men and 10.0% (n = 19) in women.

The prevalence of any-grade, grade 1 and grade 2 / 3 VFs in men and women at each BMI category are given in Table 2. BMI was associated with an increased likelihood of prevalent any-grade VF in women (OR = 1.09, $p = 0.006$, 95% CI 1.02 – 1.17). Compared to normal weight women, obese women were more likely to have at least one VF (OR = 2.65, $p = 0.025$) and at least one grade 1 VF (OR = 4.39, $p = 0.005$). No association between BMI

and grade 2 and/or 3 VF was identified in women (Table 3). Women with VFs had higher weight (p=0.002) and BMI (p<0.001) than those without (Table 4). No anthropometric differences were identified between women with and without grade 2 and/or 3 VFs.

In men, a higher BMI increased the likelihood of a prevalent grade 2 and/or 3 VF (OR = 1.08, $p$ = 0.054, 95% CI 1.00 – 1.17), and men in the obese category were more likely to have a grade 2 and/or 3 VF (OR = 3.36, $p$ = 0.032) (Table 3). No significant differences were identified in the anthropometric characteristics of men with and without any grade VF or grade 2 and/or 3 VF (Table 4).

In women, femoral neck BMD/ weight was negatively associated with prevalent grade 1 vertebral deformity only (OR 0.11, $p$=0.004). There appeared to be a relationship between LS BMD/ weight and grade 1 VF prevalence in women (OR 0.04, $p$=0.080), although the association was not statistically significant. No association between lumbar spine or femoral BMD/ weight and the likelihood of prevalent VF was identified in men.

In women, the number of prevalent VFs was associated with increasing body weight (R = 0.25, $p$ < 0.001), BMI (R = 0.22, $p$ < 0.001), lumbar spine BMD (R = 0.15, $p$ = 0.042) and femoral neck BMD/ weight (R = - 0.15, $p$ = 0.04). The number of grade 1, but not grade 2 / 3, deformities were positively associated with body weight (R = 0.28, $p$ < 0.001), BMI (R = 0.26, $p$ < 0.001), lumbar spine BMD (R = 0.18, $p$ = 0.013), and femoral neck BMD/weight (R = - 0.22, $p$ = 0.003). In men, the number of grade 1 vertebral deformities were associated with higher body weight (R = 0.17, $p$ = 0.042).

**Table 2**. Bone mineral density (BMD)/ weight and prevalent vertebral fracture across BMI categories in men and women aged 62 years.

| | **Women** | | | **Men** | | |
|---|---|---|---|---|---|---|
| | Normal weight n = 64 | Overweight n = 68 | Obese n = 58 | Normal weight n = 35 | Overweight n = 74 | Obese n = 43 |
| | BMD *(mean ± SD)* | | | | | |
| Femoral neck BMD ($g/cm^2$) | 0.911 ± 0.136 | 0.903 ± 0.145 † | 0.973 ± 0.140 † | 0.919 ± 0.151 | 0.959 ± 0.137 | 0.936 ± 0.133 |
| Lumbar spine BMD ($g/cm^2$) | 1.074 ± 0.168† | 1.073 ± 0.164† | 1.198 ± 0.185† | 1.166 ± 0.147 | 1.221 ± 0.173 | 1.206 ± 0.141 |
| | BMD : Weight Ratio *(mean ± SD)* | | | | | |
| Femoral neck BMD / weight ($g/cm^2$ : kg) | 1.50 ± 0.21* | 1.27 ± 0.23* | 1.09 ± 0.19* | 1.36 ± 0.32* | 1.17 ± 0.19* | 0.93 ± 0.13* |
| Lumbar spine BMD / weight ($g/cm^2$: kg) | 1.77 ± 0.25* | 1.52 ± 0.30* | 1.35 ± 0.23* | 1.71 ± 0.29* | 1.50 ± 0.26* | 1.20 ± 0.16* |
| | Number (%) with prevalent vertebral fracture (≥1) | | | | | |
| Any grade VF | 12 (18.8%) | 13 (19.1%) | 23 (39.7%) | 14 (40%) | 37 (50%) | 22 (51.2%) |
| Grade 1 VF | 6 (9.4%) | 11 (16.2%) | 20 (34.5%) | 12 (34.3%) | 27 (36.5%) | 19 (44.2%) |
| Grades 2 and/or 3 VF | 8 (12.5%) | 4 (5.9%) | 7 (12.1%) | 7 (20%) | 18 (24.3%) | 16 (37.2%) |

† indicates significant variance between two groups i.e. 1 vs. 2 ($p < 0.05$).

* indicates significant variation between all groups i.e. 1 vs. 2, 1 vs. 3, 2 vs. 3 ($p < 0.05$).

**Table 3**. Sex-specific odds ratios for the likelihood of prevalent vertebral fracture (VF) by BMI category

| | Any grade VF | | Grade 1 | | Grade 2 and/or 3 | |
|---|---|---|---|---|---|---|
| | Women | Men | Women | Men | Women | Men |
| | Odds ratio – Likelihood of prevalent VF vs. normal weight<br>*OR (95% Confidence interval)* | | | | | |
| Overweight (25.0 – 29.99 kg/m$^2$) | 1.0 (0.43 – 2.50) | 1.49 (0.64 – 3.48) | 1.9 (0.66 – 5.52) | 0.99 (0.42 – 2.36) | 0.44 (0.13 – 1.56) | 1.45 (0.51 – 4.12) |
| Obese (30.0 kg/m$^2$ or above) | 2.65* (1.13 – 6.20) | 1.91 (0.73 – 4.99) | 4.39* (1.57 – 12.28) | 1.59 (0.61 – 4.20) | 0.93 (0.30 – 2.89) | 3.36* (1.11 – 10.16) |

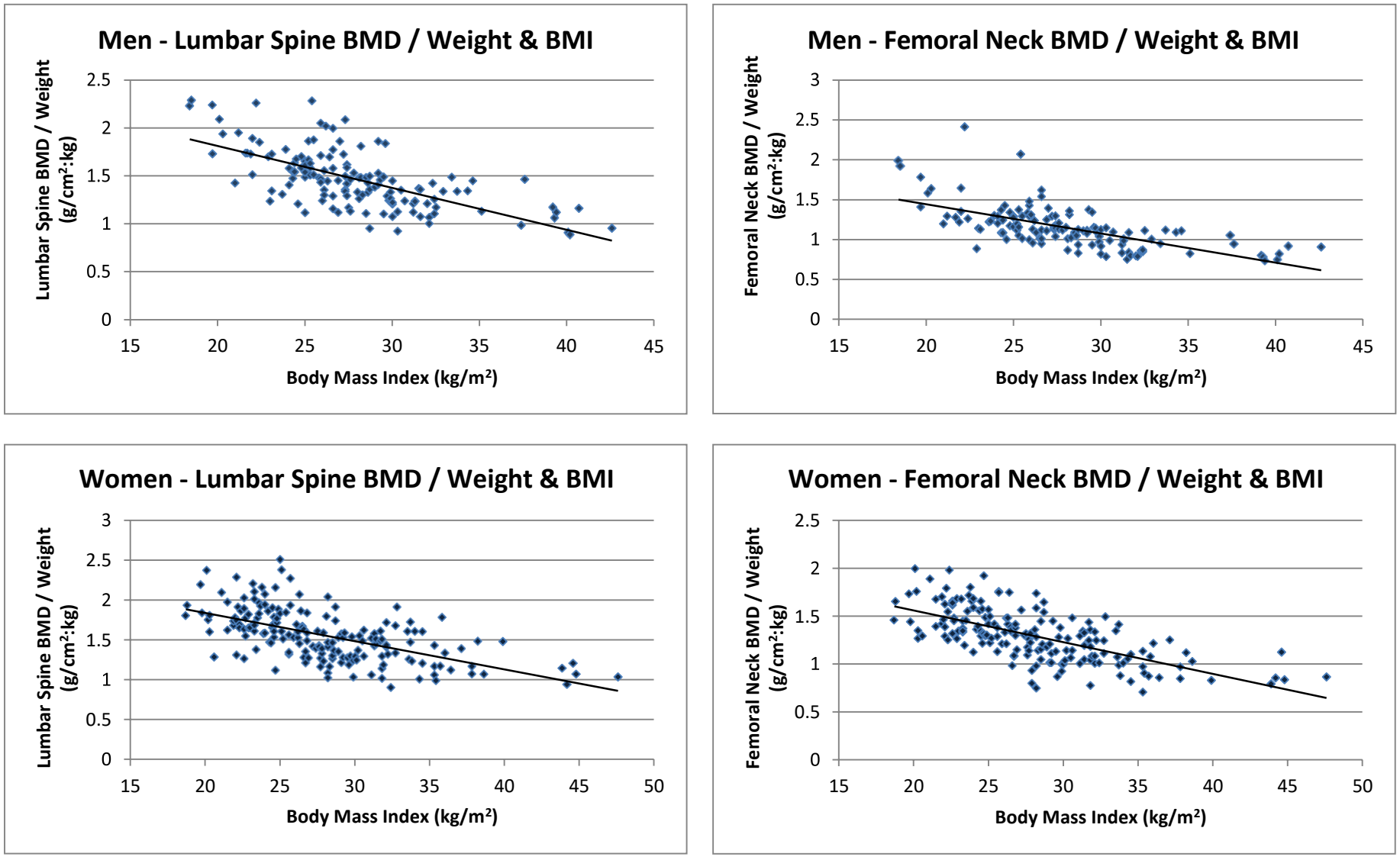
* indicates result significant vs. normal weight reference group ($p < 0.05$).

**Table 4.** Descriptive results for men and women with and without any grade and grade 2 and/or 3 VFs.

| | **Women** | | | | **Men** | | | |
|---|---|---|---|---|---|---|---|---|
| | No VF n = 142 | Any grade VF n = 48 | No grade 2 or 3 VF n = 171 | Grade 2or 3 VF n = 19 | No VF n = 78 | Any grade VF n = 74 | No grade 2or 3 VF n = 111 | Grade 2 or 3 VF n = 41 |
| Height (cm) | 162.2 ± 6.7 | 161.9 ± 7.6 | 162.3 ± 7.0 | 160.6 ± 6.5 | 173.0 ± 7.6 | 174.0 ± 6.7 | 173.5 ± 7.4 | 173.5 ± 6.5 |
| Body weight (kg) | 71.8 ± 13.8* | 79.7 ± 17.2* | 73.5 ± 14.9 | 76.7 ± 16.9 | 82.8 ± 15.6 | 86.0 ± 14.8 | 83.3 ± 15.08 | 87.1 ± 15.5 |
| BMI ($kg/m^2$) | 27.3 ± 4.7* | 30.1 ± 6.3* | 27.8 ± 5.0 | 29.2 ± 7.6 | 27.7 ± 5.0 | 28.4 ± 4.4 | 27.7 ± 4.71 | 28.9 ± 4.63 |
| Femoral neck BMD ($g/cm^2$) | 0.922 ± 0.144 | 0.945 ± 0.139 | 0.923 ± 0.142 | 0.967 ± 0.148 | 0.946 ± 0.155 | 0.942 ± 0.123 | 0.950 ± 0.146 | 0.929 ± 0.119 |
| Lumbar spine BMD ($g/cm^2$) | 1.100 ± 0.181 | 1.147 ± 0.176 | 1.111 ± 0.182 | 1.127 ± 0.163 | 1.201 ± 0.165 | 1.209 ± 0.156 | 1.207 ± 0.164 | 1.200 ± 0.151 |
| FRAX Major Osteoporotic Fracture | 8.25 ± 3.96 | 8.02 ± 3.46 | 8.19 ± 3.89 | 8.27 ± 3.27 | 7.04 ± 4.23 | 6.41 ± 3.34 | 6.78 ± 3.92 | 6.64 ± 3.64 |
| Femoral neck BMD /weight ($g/cm^2$ : kg) | 1.31 ± 0.26 | 1.23 ± 0.29 | 1.29 ± 0.26 | 1.31 ± 0.32 | 1.18 ± 0.30 | 1.12 ± 0.22 | 1.17 ± 0.27 | 1.09 ± 0.24 |
| Lumbar spine BMD /weight ($g/cm^2$ : kg) | 1.57 ± 0.31 | 1.50 ± 0.33 | 1.55 ± 0.32 | 1.54 ± 0.34 | 1.50 ± 0.32 | 1.44 ± 0.28 | 1.49 ± 0.31 | 1.41 ± 0.29 |

* indicates significant difference in mean values ($p<0.05$).

**Figure 1**. Bone mineral density (BMD)/ weight and BMI in men and women aged 62 years.



## Discussion

The aim of this study was to investigate associations between BMI, BMD relative to body weight and prevalent VF in men and women aged 62 years. It is well-established that low BMI increases the risk of osteoporosis and fracture, but the skeletal risks associated with obesity are unclear. Our primary finding was that obese men and women have a greater likelihood of prevalent VF than their non-obese counterparts. Additionally, our results indicate that BMD is reduced in obese individuals, when considered relatively to body weight, which may contribute to VF formation in this group.

In agreement with reports elsewhere, the prevalence and number of VFs were greater in men than women (19). The overall prevalence of VF we observed was comparable to previous cohorts of men, although lower in women which may reflect an age-effect (25.3% vs. 37% by Laslett *et al*.) (15). The majority of VFs in women were grade 1 deformities, which were positively associated with BMI. Although grade 2/3 VFs reflect worsening architectural deterioration of bone (30, 31), grade 1 deformities have been proven to be important predictors of future VF (8). No associations between obesity and grade 2/3 VF were identified in women. However, we observed a relatively low number of grade 2/3 VFs in women and the study may have lacked the power to identify any potential relationship.

To date, there have been few studies examining risk factors for VF in older men, and findings have been conflicting (19, 20, 32-34). In the current study, we found that a high BMI increased the likelihood of prevalent grade 2/3 VF in men, with obese men three times more likely than normal weight men to have at least one grade 2/3 VF. Results from large, prospective cohorts examining obesity and VF in women have also varied (35-37). Compston *et al.* reported that high BMI was associated with lower rates of clinically reported incident VF (35). However, using radiographs, Tanaka *et al.* found a higher risk of incident VF in

overweight and obese women compared to normal weight women (37). We observed that women with a higher BMI had an increased likelihood of any grade prevalent VF, corroborating the findings of both Laslett *et al.* and Pirro *et al*. (11, 19), and that obese women were more than twice as likely to have a prevalent VF. In agreement with previous studies, we also found that the number of VFs were positively associated with BMI in women (11, 19).

Women and men with an overweight BMI were not found to be significantly more likely than normal weight counterparts to have prevalent VFs. This could indicate that the fracture risk is greatest in underweight and obese individuals, whilst overweight individuals are predisposed to VF to a lesser extent. At present this is speculative and longitudinal analysis of VF incidence would be required to establish the gradient of risk across all four BMI categories.

There have been a number of proposed explanations for the increased risk of VF with obesity. It is possible that vertebral injuries sustained earlier in life, perhaps as a result of occupational trauma, may become aggravated by the effects of obesity as age increases, although this cannot be deduced from the current cross-sectional analysis. Postural stability is reduced in obese individuals (38), which brings an increased risk of falling (39, 40), and heavier individuals will generate greater forces on impact. VFs can also be low-trauma injuries that develop insidiously as a result of sustained compressive forces on the vertebrae, which are of the greater magnitude in the obese individual (41). In addition, obesity is associated with total and visceral adiposity, and adipocyte-derived hormones and pro-inflammatory cytokines can negatively impact bone metabolism (42).

The most pertinent explanation may be that the relationship between BMI and BMD is non-linear, with increased in BMD in obese individuals not commensurate to increased

body mass. It is well established that BMD is higher in normal weight individuals, when compared to underweight, conferring a protective advantage in the context of fracture risk (14). However, our results would suggest this trend does not continue as BMI moves into the overweight and obesity categories. We observed no significant variation in absolute BMD between males of differing BMI group, and no increase between normal weight and overweight women. Furthermore, when considered relative to body weight, we observed that BMD was significantly lower in overweight and obese men and women. These results add to a growing body of evidence highlighting that bone density does not increase proportionally with body mass in obesity. Sornary Rendu *et al.* observed various measures of bone strength to be relatively lower in obese postmenopausal women (43), whilst Beck et al found that femoral BMD had scaled upwards in proportion with increases in lean tissue mass, rather than increases in fat mass or total body mass (44). Lower femoral neck BMD/weight was associated with an increased likelihood prevalent VF in women, but not men. We propose that examining BMD relative to body weight is a useful measure when exploring bone fragility in obese populations and further research on the clinical utility of this index is warranted.

Previous studies validating the use of FRAX in predicting future VF reported that femoral neck BMD, age and self reported fracture history were the main contributing factors in generating 10-year risk score (45). The narrow age-range of this cohort, in combination with adjustment for lumbar spine BMD in regression models, is therefore likely to have limited the ability of the FRAX tool to discern high- from low-risk individuals. Further analysis of the FRAX scoring in longitudinal studies will be required to further assess its role in predicting VF.

There are a number of limitations to our study. First, we were unable to assess time since the fracture or antecedent factors relating to vertebral fracture and are unable to make

any inferences about cause and effect relationships. Longitudinal investigations are needed to address causality. Second, this cohort was, on average, overweight and therefore some results may not be generalisable to populations with a lower prevalence of obesity. Finally, caution should be taken when making inferences given that the study was performed among members of a birth cohort born in Newcastle upon Tyne, UK who were aged 61 - 63 years. However, this age group has particular public health importance because the risk of fracture is increased compared to younger ages, and effective risk factor modification (e.g. exercise and diet for fat loss) is still likely to be viable.

In conclusion, obesity appears to increase the likelihood of prevalent VF in both men and women, and we observed an increased prevalence of VF in men from this cohort. BMD was relatively low in obese individuals, when expressed relative to body weight, and therefore although absolute BMD increases in obesity, this may not be commensurate to increased body mass and fat mass. Given the rising global rates of obesity (1), the association between BMD/weight and vertebral fracture risk warrants further and timely investigation.

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Authorship and Disclosure Form